

**BIOGRAPHICAL SKETCH**

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NAME: Li, Rong

POSITION TITLE: Professor of Molecular Medicine

eRA COMMONS USER NAME (credential, e.g., agency login): RL2TRL2T

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Fudan University, Shanghai, PR China	B.S.	07/1985	Genetics
University of California, Berkeley, CA	Ph.D.	05/1991	Molecular Biology
University of California, Berkeley, CA	Postdoctoral	12/1993	DNA Tumor Viruses
Cold Spring Harbor Lab, Cold Spring Harbor, NY	Postdoctoral	08/1996	Cancer Biology

**A. Personal Statement**

My research focuses on breast cancer biology. In collaboration with Dr. Tyler Curiel and others, my group recently discovered a phosphotyrosine switch for the antitumor activity of ER $\beta$ , which paves the way for the current proposal. In addition, my laboratory previously demonstrated the transcriptional regulatory and chromatin remodeling activities of the breast cancer susceptibility gene product BRCA1, and their connections with the tissue-specific tumor suppression function of BRCA1. We also discovered a novel transcription regulator, cofactor of BRCA1 (COBRA1), which physically and functionally interacts with BRCA1 during mammary gland development and tumorigenesis. Another program in my laboratory focuses on the impact of stroma on breast cancer development and progression. In this regard, we recently demonstrated the importance of mechanical force in regulating endocrine and paracrine functions of breast stroma. I have published close to 70 scientific papers, many in high-impact journals including *Nature*, *Cell*, *Genes Dev*, *Cell Rep*, *Nat Commun*, *PNAS*, and *J Clin Invest*. Four of my publications have been cited over 100 times. I have served on several NIH study sections and other review panels for federal and private funding agencies. I am currently a regular member on the NIH Tumor Microenvironment (TME) study section. I serve on the Program Committee of the San Antonio Breast Cancer Symposium, the world's largest breast cancer symposium. I have been the Co-Leader of the Cancer Development and Progression (CDP) Program of the NCI-designated Cancer Therapy and Research Center (CTRC) since 2008.

**B. Positions and Honors****Professional Experience:**

1996-2002	Assistant Professor of Biochemistry and Molecular Genetics, University of Virginia (UVa)
2002-2006	Associate Professor (with tenure) of Biochemistry and Molecular Genetics, UVa
2007-present	Professor of Molecular Medicine, University of Texas Health Science Center at San Antonio
2008-present	Co-Leader, Cancer Development & Progression, Cancer Therapy & Research Center (CTRC) at The University of Texas Health Science Center at San Antonio (UTHSCSA)
2009-present	Member, Executive Committee, CTCRC at UTHSCSA
2011	Chair, Postdoctoral Affairs Committee, Graduate School of Biomedical Sciences, UTHSCSA

**Professional Services:**

1998	Dutch Cancer Society (ad hoc)
2000-2003	NIH CDF6 Study Section (ad hoc)
2004-2005	NIH Biochemistry Study Section (ad hoc)
2002-2007	DOD Breast Cancer Research Program (ad hoc)
2008	Susan G. Komen for the Cure Promise Grant Review
2005-2009	Regular Member, NIH Molecular Genetics A Study Section
2009	NIH Special Emphasis Panel ZCA1 (ad hoc)
2009	Editorial Board of Breast Cancer – Targets and Therapy
2009	Impact Award (IMPA) Peer Review Panel, 2009 DOD Breast Cancer Research Program.
2010-2011	NIH Tumor Microenvironment (TME) Study Section (Ad Hoc)
2010-2013	Editorial Board Member, Journal of Stem Cell & Therapy – Open Access.
2011-2013	San Antonio Breast Cancer Symposium (SABCS) Program Committee
2011	Member, Faculty Recruitment and Retention Committee, UTHSCSA
2011	Member, San Antonio Cancer Prevention and Research Institute of TX (CPRIT) Taskforce
2012-2014	Vice President for Research (VPR) Advisory Committee, UTHSCSA
2014-present	Associate Editor, Molecular Carcinogenesis
2014-2020	Regular Member, NIH Tumor Microenvironment Study Section

#### Honors and Awards:

1986-1987	Chinese-US Biochemistry Examination and Application (CUSBEA) Scholarship
1989	Taiwan Travel Foundation, Taiwan Travel Grant
1986-1989	University of California, Berkeley, International Student Fellowship
1989-1990	University of California, Berkeley, Frank Schwabacher Scholarship
1994-1997	Leukemia Society of America Special Fellow Award
1998-2000	March of Dimes, Basil O'Connor Award
1999	University of Virginia School of Medicine, The Basic Sciences Teaching Award
2005	Academy of Distinguished Educators, University of Virginia School of Medicine
2009	President's Council Excellence Award, Univ. of TX Health Science Center San Antonio

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## C. Contribution to Science

### 1. Crosstalk between transcription, DNA replication, and DNA repair

My early research focuses on a fundamental question in chromosomal transactions: *how do machineries of transcription, DNA replication, and DNA repair coordinate with each other to ensure efficient gene expression, faithful duplication of the genome, and genetic stability?* Using DNA tumor viruses, budding yeast, and mammalian cell culture as model systems, my work demonstrates that site-specific transcription factors facilitate DNA synthesis by (1) directly interacting with DNA replication proteins and (2) overcoming the nucleosomal impediment. These studies, in which I was the primary investigator, provide one of the first mechanistic insights into the crosstalk between different chromosomal events in eukaryotic cells. Combining biochemistry and cell biological tools, I also discovered an important role of cell cycle regulators in differential control of DNA replication and DNA repair in response to genotoxic agents. The early investigation of intricate interplay between different chromosomal transactions provides a compelling foundation for my current research aimed at elucidating the impact of these fundamental chromosomal events on endocrine-related tissue development and pathologies.

- a. Li R and Botchan MR. (1993) The acidic transcriptional activation domains of VP16 and p53 bind the cellular replication protein A and stimulate in vitro BPV-1 DNA replication. **Cell** 73: 1207-21.
- b. Li R, Waga S, Hannon GJ, Beach D, and Stillman B. (1994) Differential effects by the p21 CDK inhibitor on PCNA-dependent DNA replication and repair. **Nature** 371: 534-7.
- c. Abramova NA, Russell J, Botchan M, and Li R. (1997) Interaction between replication protein A and p53 is disrupted after UV damage in a DNA repair-dependent manner. **Proc Natl Acad Sci USA** 94: 7186-91. PMCID: PMC23787.

- d. Hu YF, Hao ZL, and **Li R.** (1999) Chromatin remodeling and activation of chromosomal DNA replication by an acidic transcriptional activation domain from BRCA1. **Genes Dev** 13: 637-42. PMID: PMC316546.

## 2. Sex- and tissue-specific tumor suppressor function of BRCA1

Women who carry cancer-predisposing germ-line mutations in *BRCA1* have significantly increased chance of developing breast and ovarian cancers. However, *it is not clear whether the DNA repair function alone is sufficient to account for the sex- and tissue-specific tumor suppression by BRCA1*. We identified a BRCA1-binding protein COBRA1, which is identical to the B subunit of NELF (NELF-B) involved in pausing of RNA polymerase II. Using mouse genetics and clinical samples from *BRCA1* mutation carriers, we discovered a previously unrecognized, *DNA repair-independent* interaction between BRCA1 and COBRA1 in mammary gland development and tumor development. In addition, we also discovered a role of BRCA1 in attenuating estrogen biosynthesis in ovarian granulosa cells. Collectively, these findings provide exciting insights into the tissue-specific function of BRCA1.

- a. Ye Q, Hu YF, Zhong H, Nye AC, Belmont AS, and **Li R.** (2001) BRCA1-induced large-scale chromatin unfolding and allele-specific effects of cancer-predisposing mutations. **J Cell Biol** 155: 911-21. (highlighted in January 2002 issue of *Nat Rev Cancer*) PMID: PMC2150890.
- b. Hu YF and **Li R.** (2002) JunB potentiates function of BRCA1 activation domain 1 (AD1) through a coiled-coil-mediated interaction. **Genes Dev** 16: 1509-17. PMID: PMC186344.
- c. Hu YF, Ghosh S, Amleh A, Yue W, Lu Y, Katz A, and **Li R.** (2005) Modulation of aromatase expression by BRCA1: a possible link to tissue-specific tumor suppression. **Oncogene** 24: 8343
- d. Nair S, Zhang X, Chiang H-C, Jahid MJ, Wang Y, Garza P, April C, Salathia N, Banerjee T, Alenazi FS, Ruan J, Fan J-B, Parvin JD, Jin VX, Hu YF\*, Li R\*. (2016) Genetic Suppression Reveals DNA Repair-Independent Antagonism between BRCA1 and COBRA1 in Mammary Gland Development. **Nat Commun** 7:10913. (\*co-corresponding authors)

## 3. Converting mechanical signals to endocrine output in breast cancer progression

Adipose stromal cell (ASC) is a major constituent of the breast and a source of tumor-promoting factors including estrogens. We recently discovered a previously unrecognized mechano-transducing pathway that links mechanical phenotype, such as cell shape and matrix rigidity, with the endocrine/paracrine output of ASCs. Combining three-dimension cell culture systems and animal models, our findings point to novel therapeutic approaches to disrupt this stroma-tumor communication.

- a. Ghosh S, Choudary A, Ghosh S, Musi N, Hu YF, and **Li R.** (2009) IKK $\beta$  mediates cell shape-induced aromatase expression and estrogen biosynthesis in adipose stromal cells. **Mol Endocrinol** 23: 662-70. PMID: PMC2675949.
- b. Ghosh S, Hu YF, and **Li R.** (2010) Cell density is a critical determinant of aromatase expression in adipose stromal cells. **J Steroid Biochem Mol Biol** 118: 231-6. PMID: PMC2826521.
- c. Ghosh S, Dean A, Walter M, Bao Y, Hu YF, Ruan J, and **Li R.** (2010) Cell density-dependent transcriptional activation of endocrine-related genes in human adipose tissue-derived stem cells. **Exp Cell Res** 316: 2087-98. PMID: PMC2900480.
- d. Ghosh S, Ashcraft K, Jahid MJ, April C, Ghajar CM, Ruan J, Wang H, Foster M, Hughes, DC, Ramirez, AG, Huang T, Fan JB, Hughes, D, Ramirez A, Hu YF, **Li R.** (2013) Regulation of adipose estrogen output by mechanical stress. **Nat Commun** 4:1821. PMID: PMC3921626.

## 4. Regulation of transcriptional activities of estrogen receptor $\alpha$ and $\beta$

Our previous work identifies COBRA1/NELF-B as a transcriptional coregulator of ER $\alpha$ . Given the fact that COBRA1 physically and functionally interacts with BRCA1, the COBRA1-BRCA1-ER $\alpha$  triangular relationship provides a molecular platform for COBRA1 and BRCA1 to co-regulate tissue-specific expression of developmentally important genes in mammary gland. In contrast to the tumor-promoting activity of ER $\alpha$ , ER $\beta$  inhibits tumor growth in multiple cancer types. Because ER $\beta$  is present in a significant percentage of cancer cases, rallying its antitumor activity could serve as a potential therapeutic approach. Our pioneer discovery of a phosphotyrosine switch for the antitumor activity of ER $\beta$  enables us to mobilize ER $\beta$  function with unprecedented precision.

- a. Aiyar SE, Sun JL, Blair AL, Moskaluk CA, Lu YZ, Ye QN, Yamaguchi Y, Mukherjee A, Ren DM, Handa H, and **Li R.** (2004) Attenuation of estrogen receptor  $\alpha$ -mediated transcription through estrogen-stimulated recruitment of a negative elongation factor. **Genes Dev** 18: 2134-46. PMCID: PMC515291.
- b. Pan H, Qin K, Guo Z, Ma Y, April C, Gao X, Andrews TG, Bokov A, Zhang J, Chen Y, Weintraub ST, Fan J-B, Wang D, Hu YF, Aune GJ, Lindsey ML, **Li R.** (2014) Negative elongation factor controls energy homeostasis in cardiomyocytes. **Cell Rep** 7:79. PMCID: PMC4277258.
- c. Yuan B, Cheng L, Chiang H-C, Xu X, Han Y, Su H, Wang L, Zhang B, Li J, Tekmal J, Li X, Xie X, Wang T, Tekmal RR, Curiel TJ, Yuan Z-Y, Elledge R, Hu YF, Ye Q, **Li R.** (2014) A phosphotyrosine switch determines the antitumor activity of ER $\beta$ . **J Clin Invest** 124:3378. (highlighted in September 2014 issues of *Cancer Discovery*). PMCID: PMC4109526.

#### Complete List of Published Work in MyBibliography:

<http://www.ncbi.nlm.nih.gov/sites/myncbi/rong.li.1/bibliography/40329040/public/?sort=date&direction=ascending>

#### D. Research Support

##### Current:

1 R01 CA206529-01A1 (Li/Curiel)	2/01/17 – 1/31/22	1.20 calendar mon.
NIH / NCI	\$314,471 (annual direct)	\$2,397,840 (total for 5 yrs)
Regulation of ER-beta Signaling in Carcinogenesis		
Overall objective is to elucidate the tumor-extrinsic function of ER $\beta$ signaling in antitumor immunity.		
Role: Contact PI		
1 R01 CA161349-01A1 (Li)	05/01/12 – 03/31/18	1.80 calendar mon.
NIH / NCI	\$210,345 (annual direct)	\$1,598,622 (total for 5 yrs)
Regulation of hormone production by matrix proteins		
Overall objective is to elucidate the role of tissue rigidity in local estrogen production in breast tissue.		
Role: PI		
1 R21 CA209154-01 (Li)	07/01/16 – 06/30/18	1.20 calendar mon.
NIH / NCI	\$150,000 (annual direct)	\$364,857 (total for 2 yrs)
Re-sensitizing ER-Alpha Mutant Breast Cancer Cells to Hormonal Therapy		
The overall objective of this proposal is to explore a novel strategy to re-sensitize breast cancer cells carrying therapeutically resistant ER $\alpha$ mutant to hormonal therapy.		
Role: PI		
5 P30 CA054174-19S5 (Thompson)	09/01/14 – 07/31/19	1.20 calendar mon.
NIH/NCI	~\$1,800,000 (total for 5 yrs)	
NCI-Designated Cancer Center		
Provides support to the CTRC for three research programs and ten shared resources to better understand the specific cancer-related risks and disease patterns in Hispanics, and to better serve the needs of our citizens.		
Role: Co-Leader of the Cancer Development and Progression Program		
RP150055 (PI: Li, Co-PI: McHardy)	12/01/14 – 11/30/17	2.40 calendar mon.
CPRIT	\$403,539 (annual direct)	\$2,000,000 (total for 3 yrs)
Druggable Targets That Regulate the Antitumor Activity of ER-beta		
The overall objective of this proposal is to explore the translational potential of a novel ER $\beta$ signaling pathway in breast cancer treatment and prevention.		
Role: PI		

RP150574 (Li)	12/01/14 – 11/30/16	0.6 calendar mon.
CPRIT	\$95,000 (annual direct)	\$200,000 (total for 2 yrs)
Turning on a Novel Tumor-Inhibiting Switch for Colorectal Cancer		
The overall objective of this proposal is to unleash the antitumor activity of ER $\beta$ in treating and preventing colorectal cancer.		
Role: PI		

RP170126 (Hu)	12/01/16-11/30/19	1.2 calendar mon.
CPRIT	\$290,000 (annual direct)	\$900,000 (total for 3 yrs)
A Novel Pathway to Reduce BRCA1-Associated Breast Cancer Risk		
The overall objective of this proposal is to investigate BRCA1 function in transcriptional regulation during mammary gland development tumorigenesis.		
Role: Co-PI		

DOD-BC130557 (Li)	06/01/14 – 05/31/17	1.00 calendar mon.
DOD	\$113,000 (annual direct)	\$571,875 (total for 3 yrs)
Molecular Basis of Parity-Associated Breast Cancer Risk Reduction		
The overall objective of this proposal is to elucidate the molecular basis of parity-associated breast cancer risk reduction.		
Role: PI		

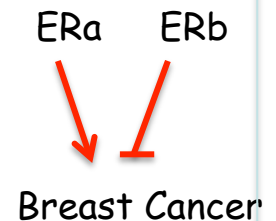
W81XWH-16-1-0294 (Tekmal)	07/01/16 – 06/30/19	0.36 calendar mon.
DOD	\$249,907 (annual direct)	
Prevention of breast cancer and therapy resistance using novel therapeutic approaches		
The overall objective of this proposal is to overcome therapeutic resistance for ER+ breast cancer.		
Role: co-I		

DOD-BC160256 (Hu/Li)	09/30/17 – 09/29/20	1.20 calendar mon.
DOD	\$72,520 (annual direct)	\$331,779 (total for 3 yrs)
Understanding Drug Resistance in BRCA1-Associated Cancer Therapy		
The overall objective of this proposal is to characterize a previously unrecognized pathway that confers therapeutic resistance in BRCA1-associated cancer treatment.		
Role: Partnering PI		

# Breast Cancer-Focused Research

- **Tissue-specific Tumor Suppressor**  
Why do germ-line BRCA1 mutations only increase breast and ovarian cancers in women?
- **ER $\alpha$  versus ER $\beta$**   
How can these two structurally similar estrogen receptors play the opposite roles in breast cancer?
- **Obesity in breast cancer**  
How do adipose homeostasis and metabolism affect breast cancer progression?



## Laboratory Strengths

- Cutting-edge science that combines **mechanistic** studies with **translational** potentials
- Longstanding history of high-impact publications
- Highly **interactive, stimulating, and fun** research environment
- Broad collaborating **network** consisting of clinicians, drug-discovering teams, and other technical experts
- **Solid and sustained** research funding

